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Recommendations for lab-based screening tests for adult women

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Women's Health

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention. Tables for this article can be found in the Digital Edition of the article that originally ran in print, available [here](#).

Health screening tests have a great impact on the public's health because they involve testing asymptomatic populations for specific diseases or health conditions for secondary prevention when interventions may halt or diminish disease progression before appearance of clinical signs and symptoms. The U.S. Preventive Services Task Force (USPSTF),¹ supported by the Agency for Healthcare Research and Quality, is widely considered to be the leading independent panel of experts in recommendations about disease prevention and in primary and secondary interventions. This organization conducts rigorous and impartial assessments of the scientific evidence for effectiveness of a broad range of clinical preventive services, including health screening.

According to the World Health Organization, all of the following criteria must be met in an effective screening program: significant societal burden; detectable asymptomatic phase; screening test accuracy; acceptability, availability, and feasibility; effective prognostication and intervention for those who screen positive; cost-effectiveness; and assurance of informed consent and patient confidentiality.² In providing recommendations, the USPSTF considers these criteria but does not strictly use them when evaluating screening tests.

For example, if a screening test has been evaluated in a randomized control trial and has been shown to result in better outcomes for those in the screening group, the USPSTF does not consider cost-effectiveness. All screening recommendations are rated by the USPSTF into one of five grades:³

- 'A' for strong recommendation with high certainty that net benefit is substantial,
- 'B' for recommendation with high certainty that net benefit is moderate or moderate certainty that net benefit is moderate to substantial,
- 'C' for individualized decision making with at least moderate evidence that net benefit is small,

- ‘**D**’ against screening with moderate to high certainty that net benefit is close to zero or harms outweigh benefits, and
- ‘**I**’ is a statement that no recommendation can be made due to available evidence that is insufficient, of poor quality, or conflicting, making it not feasible to objectively evaluate the net balance between health benefits and harms of screening.

Health screening should be offered or provided for **A** and **B** recommendations. **C** recommendation implies that screening should be offered or provided for selected patients depending on individual circumstances.³ For **D** recommendation, screening should be discouraged. For **I** recommendation, if screening is offered, patients should understand the uncertainty about the balance of health benefits and harms.⁴

In this article, the recommendations of the USPSTF for all laboratory-based screening tests for or relevant to adult women are presented, along with a brief rationale based on evaluation of the balance of health benefits and harms. Some of these recommendations apply to both men and women, and they are also included. When applicable, specific CDC recommendations are also described. A previous article had described selected laboratory-based screening tests for aging males.⁵ Laboratory screening tests described are those used for the risk of coronary heart disease; endocrine and metabolic disorders (chronic kidney disease, diabetes mellitus, hereditary hemochromatosis, and thyroid disease); infectious diseases caused by chlamydia, genital herpes, gonorrhea, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis; cancer of the bladder, cervix, colon and rectum, lung, ovaries, and pancreas; and substance abuse. This article is meant to provide the reader with an understanding and appreciation of whether and why specific laboratory screening tests should or should not be used for the evaluated diseases or conditions, sometimes using different target populations. The tables (see digital version) list the USPSTF recommendations for screening of the diseases or conditions relating to adult women, along with the recommendation grade for each. Recommendations for laboratory screening tests for risk of coronary heart disease; endocrine and metabolic disorders, and during pregnancy; infectious diseases; neoplastic diseases; and substance abuse are presented and discussed.

Risk of Coronary Heart Disease

For women aged 20 and older at increased risk for coronary heart disease, there is good evidence that lipid-lowering drug therapy substantially decreases incidence of coronary heart disease in those with abnormal lipids, and there is good evidence that harms from screening and treatment are small and include possible labeling and adverse effects associated with lipid-lowering therapy such as rhabdomyolysis (**A** recommendation for women 45 years of age or older and **B** recommendation for those between 20 and 44 years of age).⁶ Good-quality evidence shows that total cholesterol, low-density lipoprotein (LDL)-cholesterol and high-density lipoprotein (HDL)-cholesterol are independent predictors of risk for coronary heart disease, and that total cholesterol/HDL-cholesterol ratio or LDL-cholesterol/HDL-cholesterol ratio classify risk better than total cholesterol alone.⁶ Although triglycerides level is a strong univariate predictor of cardiovascular events, its association

with these events is reduced substantially by adjustment for other risk factors. For women aged 20 and older who are not at increased risk for coronary heart disease, individualized decision making is recommended, given that there is at least moderate evidence that net benefit of screening is small (C recommendation). High-sensitivity C-reactive protein (CRP) has been the most rigorously studied nontraditional marker for risk of coronary heart disease. However, on the basis of the latest USPSTF review, there is inconclusive evidence that considering changes in CRP level lead to primary prevention of coronary heart disease events (I recommendation).⁷ Analyses from four large cohorts were consistent in finding evidence that including CRP improves risk stratification among initially intermediate-risk persons, that CRP has desirable test characteristics, and that good data exist about the prevalence of elevated CRP levels in intermediate-risk persons.⁸ However, limited evidence links changes in CRP levels to primary prevention of cardiovascular events. Other laboratory risk markers evaluated by the USPSTF were lipoprotein(a), homocysteine, leukocyte count and fasting blood glucose. Current evidence, however, does not support routine use of any of these markers for further risk stratification of intermediate-risk persons, and there is little evidence to determine harms of using nontraditional markers to screen for risk of coronary heart disease. Potential harms of screening include lifelong use of medications without proven benefit and psychological harms from being misclassified in a higher risk category.

Endocrine/Metabolic Disorders and Pregnancy

Endocrine and Metabolic Disorders

Chronic kidney disease—No clinical trials have evaluated the screening or monitoring of chronic kidney disease; therefore, evidence that routine screening improves clinical outcomes for asymptomatic adults is inadequate (I recommendation).^{9,10} Although potential harms of screening may include adverse effects from venipuncture and psychological effects of labeling a person with the disease, evidence on the harms of screening is inadequate.⁹ Patients falsely identified as having the disease, by being tested for urinary protein and serum creatinine, may receive unnecessary treatment and diagnostic interventions resulting in harmful effects given that there is convincing evidence that medications used to treat early disease may have adverse effects.⁹

Diabetes mellitus—Direct evidence is lacking on the health benefits of detecting type 2 diabetes by either targeted or mass screening, and indirect evidence also fails to demonstrate health benefits for screening the general population.¹¹ However, individuals with hypertension probably benefit from screening because blood pressure targets for those with diabetes are lower than those without diabetes; and in those with hypertension and diabetes, lowering blood pressure below conventional target values reduces the incidence of cardiovascular events and mortality.¹² Intensive glycemic control in persons with clinically detected diabetes mellitus reduces progression of microvascular disease. Screening for type 2 diabetes every three years in asymptomatic adults with sustained blood pressure (either treated or untreated) of greater than 135/80 mm mercury is recommended (B recommendation).¹³ In addition to criteria for plasma or blood glucose measurement, diabetes may also be diagnosed by demonstrating increased blood hemoglobin A1c

concentrations.¹⁴ Observational studies report no serious long-term adverse psychological effects such as anxiety from receiving a new diagnosis of type 2 diabetes mellitus from screening.¹² However, longer-term effects of labeling a large proportion of the population as abnormal are unknown. For adults with blood pressure of 135/80 mm mercury or lower, there is inadequate evidence that early diabetes control as a result of screening provides an incremental benefit for microvascular clinical outcomes compared with initiation of treatment after clinical diagnosis given that the benefits of tight glycemic control on microvascular clinical outcomes, such as severe visual impairment or end-stage renal disease, take years to become apparent (**I** recommendation).¹²

Hereditary hemochromatosis—Although available data suggest that 38%-50% of C282Y homozygotes develop iron overload and 10%-25% develop some type of hemochromatosis-associated morbidity, current research provides very limited numbers of observations and research designs are subject to bias.¹⁵ There is fair evidence that clinically important disease due to hereditary hemochromatosis is rare in the general population, and that a low proportion of individuals with a high-risk genotype (C282Y homozygotes) manifest the disease.¹⁶ Even among these individuals, it appears that only a small subset will develop symptoms of hemochromatosis, and an even smaller proportion of them will develop advanced stages of clinical disease. Also, the risk of iron overload is reduced further for pre-menopausal women due to the monthly menstrual blood loss. There is poor evidence that early therapeutic phlebotomy, the primary treatment for hemochromatosis, improves morbidity and mortality in screening-detected versus clinically detected individuals.¹⁶ Screening could lead to identification of a large number of individuals who possess high-risk genotype but may never manifest clinical disease, and this may result in unnecessary surveillance, treatments and invasive work-up, labeling and anxiety. Potential harms of genetic screening for hereditary hemochromatosis appear to outweigh its potential benefits (**D** recommendation).¹⁶

Thyroid disease—Screening for occult thyroid dysfunction in adults using tests for thyroxine (T4) and thyroid-stimulating hormone (TSH) would be valuable if there were clinical benefits of early treatment, including relief of previously unrecognized symptoms.¹⁷ Although there is fair evidence that TSH testing can detect subclinical thyroid disease in people without symptoms of thyroid dysfunction, there is poor evidence that treatment improves clinically important outcomes in adults with screen-detected thyroid disease (**I** recommendation).¹⁸ Although yield of screening is greater in certain high-risk groups, such as postpartum women as well as those with Down syndrome and the elderly, there is poor evidence that screening these groups leads to clinically important benefits; and evidence regarding the efficacy of treatment in women found by screening to have subclinical thyroid dysfunction is inconclusive.¹⁹ Data on adverse effects of the broader use of levothyroxine are sparse,¹⁹ and there is potential for harm caused by false positive screening tests even though the magnitude of harm is unknown.¹⁸ As an initial screen for thyroid disease, sensitive TSH testing offers the greatest promise.¹⁷

Screening During Pregnancy

Bacterial vaginosis—For pregnant women at low risk for preterm delivery, there is moderate certainty that screening for bacterial vaginosis has no net benefit (**D** recommendation).²⁰ For pregnant women at high risk for preterm delivery, evidence is conflicting and the balance of benefits and harms cannot be determined (**I** recommendation).

Bacteriuria—In pregnant women, convincing evidence indicates that detection of and treatment for asymptomatic bacteriuria with antibiotics significantly reduces the incidence of symptomatic maternal urinary tract infections and low birth weight (**A** recommendation).²¹ Potential harms associated with treatment for asymptomatic bacteriuria include adverse effects from antibiotics and development of bacterial resistance.

Chlamydial infection—There are no studies evaluating effectiveness of screening for chlamydial infection in pregnant women who are at increased risk of infection. However, screening identifies infection in asymptomatic pregnant women, there is a high prevalence of infection among pregnant women at increased risk of infection, and fair evidence of improved pregnancy and birth outcomes for women treated for chlamydial infection (**B** recommendation).²² Potential harms of screening include anxiety and various problems arising from positive results and over-treatment. Screening with nucleic acid amplification testing of urine or vaginal swabs is recommended at the first prenatal visit, and for patients with continuing or new risk of infection, screening is also recommended during the third trimester.²²

Genital herpes simplex virus (HSV) infection—Screening asymptomatic pregnant women using serological screening tests for HSV antibody does not reduce transmission of genital HSV to newborn infants, and there is no evidence that treating seronegative women decreases risk for neonatal infection.²³ There is limited evidence that performance of Caesarean section in women with active HSV lesions at the time of delivery decreases neonatal HSV infection. There is limited evidence of safety of antiviral therapy in pregnant women and neonates.²³ Potential harms of screening include false-positive test results, labeling, and anxiety, as well as false negative tests resulting in false reassurance. The potential harms of screening for genital HSV infection outweigh potential benefits (Shahram Shahangian recommendation).²³

Gestational diabetes mellitus—There is adequate evidence that treatment of screen-detected gestational diabetes mellitus (**B** recommendation) with dietary modifications, glucose monitoring and insulin if needed can significantly reduce the risk of preeclampsia, fetal macrosomia and shoulder dystocia.²⁴ When these outcomes are considered collectively, there is a moderate net benefit for both mother and infant.

Gonorrhea infection—Pregnant women with gonorrhea infection are at higher risk for premature rupture of membranes, preterm labor, chorioamnionitis, and perinatal transmission to infants can cause severe conjunctivitis resulting in blindness if untreated.²⁵ There is fair evidence that screening tests (culture and nucleic acid amplification tests of endocervical swabs, or nucleic acid amplification tests of urine or vaginal swabs) can

accurately detect gonorrhea infection, good evidence that antibiotics can cure the infection, and fair evidence that screening pregnant women at high risk for gonorrhea may prevent the complications associated with gonococcal infection during pregnancy (**B** recommendation).²⁵ Although no study has directly examined harms of screening or treatment for gonorrhea infection, potential harms may include opportunity costs to the clinician and patient (time and other resources); stress, labeling and further testing due to positive or false-positive test results; and harms resulting from adverse drug reactions. At-risk pregnant women should be screened at first prenatal visit, and for those at continued risk or with a new risk factor, a second screening should be conducted during the third trimester.²⁵ In women, gonorrhea is a major cause of cervicitis and pelvic inflammatory disease, which can lead to ectopic pregnancy, infertility and chronic pelvic pain. However, prevalence of gonorrhea infection in pregnant women not at increased risk of infection is low, and the balance between benefits and harms of screening in pregnant women not at increased risk of infection cannot be determined (**I** recommendation).

Hepatitis B virus (HBV) infection—Screening for HBV infection in pregnant women to identify newborns who will require prophylaxis against perinatal infection is a well-established, evidence-based standard of current medical practice (**A** recommendation).²⁶ A 2006 systematic review of randomized, controlled trials found that newborn prophylaxis reduced perinatal transmission of HBV infection. There is good evidence that universal prenatal screening for HBV infection using hepatitis B surface antigen (HBsAg) test substantially reduces prenatal transmission of HBV and subsequent development of chronic HBV infection.²⁷ Current practice of providing post-exposure prophylaxis with hepatitis B immune globulin administered at birth to infants of mothers infected with HBV substantially reduced risk for acquiring HBV infection.²⁶ HBsAg test should be ordered at first prenatal visit, and pregnant women with unknown HBsAg test status or with new or continuing risk factors at admission to hospital, birth center or other delivery setting should be (re-)screened.²⁶ Although potential harms of screening are no greater than small, there are no published studies that describe harms of screening for HBV infection in pregnant women.²⁶

Human immunodeficiency virus (HIV) infection—There is convincing evidence that identification and treatment of HIV-positive pregnant women dramatically reduces rates of mother-to-child transmission.²⁸ However, no study has directly evaluated the effects on clinical outcomes of screening versus no screening for HIV infection.²⁹ Antiretroviral therapy in combination with avoidance of breastfeeding and elective Caesarean section in women with viremia reduces risk for mother-to-child transmission.³⁰ There is convincing evidence that individual antiretroviral drugs, drug classes, and combinations are all associated with increased risk for cardiovascular and some short-term adverse events such as increased risk of preterm delivery during pregnancy, but the magnitude of such risks appears to be small.²⁸ Evidence is insufficient to determine optimum time intervals for HIV screening; however, a reasonable approach is one-time screening of all pregnant women to identify women who are already HIV-positive, with repeated screening of those known to be at increased risk of HIV infection (**A** recommendation).²⁸

Iron deficiency anemia—There is fair evidence that treating asymptomatic pregnant women who have iron deficiency anemia results in moderate benefits in health outcomes (**B** recommendation).³¹ However, there is no evidence addressing harms of screening pregnant women for iron deficiency anemia. Potential harms include false-positive results, anxiety, cost, gastrointestinal symptoms, and unintentional overdose.³¹

Lead poisoning—Given the significant potential harms of treatment and residential lead hazard abatement and no evidence of treatment benefit, the USPSTF concluded that harms of screening for elevated blood lead levels in asymptomatic pregnant women outweigh potential benefits (**D** recommendation).³²

Rh (D) incompatibility—The USPSTF found good evidence that D blood typing, anti-D antibody testing and intervention with Rh(D) immunoglobulin, as appropriate, prevents maternal sensitization and improves outcomes for newborns, and these benefits substantially outweigh any potential harm.³³ Therefore, it is strongly recommended that all pregnant women undergo D blood typing and antibody testing during their first prenatal visit (**A** recommendation). There is fair evidence that repeated antibody testing for unsensitized D-negative women (unless the father is also known to be D-negative) and intervention with D immunoglobulin, as appropriate, provides additional benefit over a single test at the first prenatal visit in preventing maternal sensitization and improving outcomes for newborns.³³ The benefits of repeated testing substantially outweigh any potential harm; therefore, the USPSTF recommends repeated D antibody testing for all unsensitized D-negative women at 24-28 weeks' gestation, unless the biological father is known to be D-negative (**B** recommendation).

Syphilis infection—Untreated syphilis during pregnancy is associated with stillbirth, neonatal death, bone deformities, and neurologic impairment; and there is adequate evidence that screening tests can accurately detect syphilis infection, and convincing observational evidence that universal screening of pregnant women decreases proportion of infants with clinical manifestations of syphilis infection.³⁴ Nontreponemal tests commonly used for initial screening are Venereal Disease Research Laboratory (VDRL) or Rapid Plasma Reagin (RPR), followed by confirmatory fluorescent treponemal antibody absorbed (FTA-ABS) or T. pallidum particle agglutination (TP-PA) tests.³⁵ All pregnant women should be tested at their first prenatal visit. Current recommendations for women in high risk groups call for screening at first prenatal visit, and again during third trimester (at 28 weeks of gestation) and at delivery.³⁶ Although there is no new direct evidence that screening for syphilis infection leads to improved health outcomes in persons at increased risk for infection, there is adequate evidence that screening tests can accurately detect syphilis infection and that antibiotics can cure syphilis.³⁵ Screening and treatment may result in potential harms, including false-positive results that require clinical evaluation, unnecessary anxiety to the patient and harms of antibiotic use.^{34,35} Drug-related harms include anaphylaxis from penicillin allergy, and Jarisch-Herxheimer reaction occurring within first 24 hours after treatment.³⁶ Screening of pregnant women is strongly recommended with high certainty that net benefit is substantial (**A** recommendation).

Screening for Infectious Diseases

Bacteriuria—In nonpregnant women, adequate evidence suggests that screening for asymptomatic bacteriuria is ineffective in improving clinical outcomes, and that there is moderate certainty that the harms of screening outweigh any potential benefits (**D** recommendation).²¹

Chlamydia—There is good evidence that screening for chlamydial infection in sexually active women ages 24 and younger or older at increased risk of infection can reduce incidence of pelvic inflammatory disease, and that benefits of screening these women are substantial (**A** recommendation).²² Potential harms include anxiety and relationship problems arising from positive results and over-treatment. The CDC recommends that these women be screened at least annually using nucleic acid amplification tests on urine or vaginal swabs.³⁷ The 2014 CDC recommendation advises use of nucleic acid amplification tests as they are better than other available tests because of their increased clinical sensitivity and specificity, and greater ease of specimen transport.³⁸

No studies were identified documenting benefits of screening women older than 24 years of age who are not at increased risk for chlamydial infection.²² While recognizing potential benefit to women identified through screening, overall benefit of screening would be small, given low prevalence of infection among women who are not at increased risk (**C** recommendation).

Genital HSV—There is no evidence that screening asymptomatic individuals with serological tests for HSV antibody improves health outcomes or that it reduces transmission of this virus.²³ There is good evidence that serological screening tests can accurately identify those exposed to HSV and that antiviral therapy improves health outcomes in symptomatic women, such as those with multiple recurrences. However, there is no evidence that use of antiviral therapy improves health outcomes in those with asymptomatic infection.²³ Potential harms of screening include false-positive test results, labeling, and anxiety, as well as false negative tests resulting in false reassurance. Harms of screening for genital HSV infection outweigh potential benefits (**D** recommendation).²³

Gonorrhea—Women with asymptomatic gonorrhea infection have high morbidity due to pelvic inflammatory disease, ectopic pregnancy, and chronic pelvic pain.²⁵ There is fair evidence that screening tests (culture and nucleic acid amplification tests of endocervical swabs, or nucleic acid amplification tests of urine or vaginal swabs) can accurately detect gonorrhea infection, good evidence that antibiotics can cure the infection, and fair evidence that screening women at high risk for gonorrhea may prevent complications associated with gonococcal infection (**B** recommendation). Although no study has directly examined harms of screening or treatment for gonorrhea infection, potential harms may include opportunity costs to the clinician and patient (time and other resources); stress, labeling, and further testing; and side effects of medications.²⁵ Optimal screening interval for non-pregnant women at increased risk for gonorrhea infection is not known.

There is a low prevalence of gonorrhea infection in the general population and consequently a low yield from screening; therefore, harms such as false-positive test results, labeling in low-prevalence populations, and adverse effects of drugs used in treatment outweigh any potential benefits (**D** recommendation).²⁵

Hepatitis B Virus (HBV)—There is no evidence that screening the general population for HBV infection improves long-term health outcomes such as cirrhosis, hepatocellular carcinoma, or mortality.²⁷ Prevalence of HBV infection is low, and the majority of infected individuals do not develop chronic infection, cirrhosis, or HBV-related liver disease. No studies were identified that addressed whether routine screening of asymptomatic individuals in clinical settings was an effective method of reducing HBV infection in the general population, and that early screening and detection of HBV infection reduced morbidity and mortality associated with chronic carrier state of HBV infection.³⁹ No studies were identified that addressed effectiveness of routine screening of high-risk individuals for purposes of referral for HBV vaccination. Potential harms of screening include labeling, and they are likely to exceed any potential benefits (**D** recommendation).²⁷

Hepatitis C virus (HCV)—There is no direct evidence on benefit of screening for HCV infection in asymptomatic adults in reducing morbidity and mortality; however, there is adequate evidence that antiviral regimens result in sustained virologic and improved clinical outcomes.⁴⁰ Given accuracy of the screening test (anti-HCV antibody testing followed by confirmatory nucleic acid amplification testing⁴¹) and availability of effective interventions for HCV infection, screening is of moderate benefit for populations at high risk and those born in 1945-1965 (**B** recommendation).⁴⁰ There is limited evidence on harms of screening for HCV; potential harms of screening include anxiety, patient labeling, and feelings of stigmatization. There is adequate evidence on harms associated with diagnostic evaluation used to guide treatment decisions such as liver biopsy; and these harms include bleeding, infection, and severe pain in approximately 1% of persons having liver biopsy and death in up to 0.1% of them.⁴⁰ While there is adequate evidence that antiviral therapy regimens may be associated with fatigue, headache, flu-like symptoms, hematologic events and rash, therapy is given only for a defined duration, and serious adverse events are uncommon and self-limited, typically resolving after treatment is discontinued.

Screening for HCV infection is recommended in adults at high risk including those with any history of intravenous drug use or blood transfusions prior to 1992.⁴⁰ Other risk factors include chronic hemodialysis, being born to an HCV-infected mother, imprisonment and intranasal cocaine and other non-injection drug use.⁴² The CDC also recommends one-time testing without prior ascertainment of HCV risk for adults born between 1945 and 1965, a population with a disproportionately high prevalence of HCV infection and related disease.⁴³ Anti-HCV antibody testing with subsequent polymerase chain reaction testing for viremia is accurate for identifying patients with chronic HCV infection.⁴⁰

Human Immunodeficiency Virus (HIV)—There is convincing evidence that identification and treatment of HIV infection is associated with a markedly reduced risk for progression to acquired immunodeficiency syndrome (AIDS), AIDS-related events, as well as death in individuals with immunologically advanced disease.²⁸ There is convincing

evidence that use of antiretroviral therapy is associated with a substantially decreased risk for transmission from HIV-positive persons to their uninfected heterosexual partners. Net benefit of screening for HIV infection (anti-HIV antibody test followed by confirmatory Western blot or immunofluorescent assay) is substantial.²⁸ However, new testing algorithms currently in use do not require performing confirmatory Western blot or immunofluorescent assay.⁴⁴

Evidence is insufficient to determine optimum time intervals for HIV screening; however, a reasonable approach is one-time screening to identify those already HIV-positive, with repeated screening if at increased risk for HIV infection.²⁸ Screening those aged 15-65 years for HIV infection as well as older individuals at increased risk for infection is recommended using repeated enzyme immunoassay and if positive, followed by confirmatory Western blot or immunofluorescence assay (**A** recommendation).²⁸ The CDC recommends at least annual screening of all individuals at high risk for HIV infection including those initiating treatment for tuberculosis or seeking treatment for sexually transmitted diseases, as well as one-time screening of all persons 13-64 years of age.⁴⁵

Syphilis—Although there is no new direct evidence that screening for syphilis infection leads to improved health outcomes in persons at increased risk of infection, there is adequate evidence that screening tests can accurately detect syphilis infection and that antibiotics can cure syphilis.³⁵ Screening and treatment may result in potential harms, including false-positive results that require clinical evaluation, unnecessary anxiety to the patient, and harms of antibiotic use.^{34,35} Drug-related harms include anaphylaxis from penicillin allergy, and Jarisch-Herxheimer reaction occurring within first 24 hours after treatment.³⁶ Screening of persons at increased risk for infection is strongly recommended with high certainty that net benefit is substantial (**A** recommendation).

There is no evidence that screening for syphilis infection leads to improved health outcomes in persons not at increased risk.³⁵ Therefore, screening is not recommended for nonpregnant persons not at increased risk of syphilis infection, and there is moderate to high certainty that harms of screening outweigh potential benefits (**D** recommendation).

Screening for Neoplastic Diseases

Bladder cancer—No randomized trials or high-quality controlled observational studies have evaluated clinical outcomes associated with screening compared with not screening for bladder cancer.⁴⁶ Although no study has evaluated the sensitivity or specificity of tests for hematuria, urinary cytology or other urinary biomarkers for bladder cancer in persons without a history of bladder cancer, positive predictive value of screening tests is less than 10% even in higher-risk populations.⁴⁶ No recommendation can be made to screen for bladder cancer given that the available evidence is insufficient at this time to objectively evaluate the net balance between health benefits and harms of screening (**I** recommendation).

Breast and ovarian cancer susceptibility—The USPSTF recommends that primary care providers screen women who have family members with breast or ovarian cancer with one of several screening tools designed to identify a family history that may be associated

with an increased risk for potentially harmful mutations in cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing (**B** recommendation).⁴⁷

The Task Force recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1* or *BRCA2* genes (**D** recommendation).⁴⁷

Cervical cancer—Given that benefits of screening substantially outweigh harms, cervical cytology every 3 years for women with a cervix who are aged 21-65 years is strongly recommended (**A** recommendation).⁴⁸ For women aged 30-65 years, a combination of cervical cytology and human papilloma virus (HPV) DNA testing every 5 years is also strongly recommended instead of cervical cytology screening every 3 years (**A** recommendation).⁴⁸ Liquid-based cytology has equivalent sensitivity and specificity to conventional cytology, and one-time HPV screening is more sensitive than cytology for detecting cervical intraepithelial neoplasia (CIN)3+/CIN2+ lesions, but it is less specific.⁴⁹

Primary HPV screening detects more cases of CIN3+ or cancers in women older than 30 years, with randomized controlled trials showing mixed results of co-testing in women aged 30 years or older compared with cytology alone, with no clear advantage over primary HPV screening.⁴⁹ However, more complete evidence is needed before HPV-enhanced primary screening is widely adopted for women aged 30 years or older.⁴⁹

Given the low prevalence of pre-neoplastic lesions in women younger than 21 years of age, harms of screening outweigh any potential benefits (**D** recommendation).⁴⁸

Also, given low prevalence of pre-neoplastic lesions in women greater than 65 years of age with adequate prior negative screenings and not otherwise at high risk of cervical cancer, harms of screening in this age group outweigh any potential benefits (**D** recommendation).⁴⁸

Harms associated with screening of women with no history of high-grade lesions or cancer of the cervix outweigh any potential benefits, particularly after hysterectomy that involves removal of the cervix, given the relatively low prevalence of vaginal cancer (**D** recommendation).⁴⁸

Colorectal cancer—There is convincing evidence that screening with fecal occult blood test reduces colorectal cancer mortality in men and women aged 50-75 years (**A** recommendation).⁵⁰ However, follow-up of positive screening test results requires colonoscopy. The primary benefit of the fecal occult blood test compared to flexible sigmoidoscopy or colonoscopy is that it may obviate their attendant risks.⁵⁰ Harms of colorectal cancer screening are due to use of invasive procedures in final evaluation of a positive test result, and they may arise from preparation of the patient for colonoscopy, sedation used during the procedure and the procedure itself, as well as anxiety, inconvenience, discomfort, and additional medical expenses. Although evidence about harms of fecal occult blood test is lacking, it is expected to be insignificant.

Fecal occult blood testing is the only diagnostic method with direct evidence for reduction of mortality.⁵⁰ Annual screening is recommended with high-sensitivity tests such as those based on fecal immunochemical methods; however, there are no new trials reporting that using these methods has an impact on mortality.

Tradeoff between superior sensitivity and reduced specificity occur with high-sensitivity guaiac tests.⁵¹ There is adequate evidence that benefits of detection and early intervention decline after age 75 years.⁵⁰ Lead time between detection and treatment of colorectal neoplasia and mortality benefit is substantial, and competing causes of mortality make it progressively less likely that this benefit will be realized in individuals between ages of 76 and 85 years (**C** recommendation).

There is adequate evidence that harms of detection and early intervention after age 85 years exceed any potential benefits due to other competing causes of mortality at this age group (**D** recommendation).⁵⁰

There are no trials that report on mortality for fecal DNA testing (**I** recommendation).⁵⁰ Fecal DNA has the potential to be a highly specific test, reducing harms associated with follow-up of false-positive test results. These tests are evolving, not widely used, and are likely to have a high monetary cost; and information on harms from fecal DNA screening is currently limited.⁵⁰

Lung cancer—Benefits of screening for lung cancer using sputum cytology or any other non-laboratory methods have not been established in any group, including asymptomatic high-risk populations such as older smokers (**I** recommendation).⁵² The balance of benefits and harms becomes increasingly unfavorable for persons at lower risk, such as nonsmokers.

Low-dose computed tomography has high sensitivity and acceptable specificity for detecting lung cancer in high-risk persons, and it is currently the only recommended screening test for lung cancer. Because of high rate of false-positive results, many patients will undergo invasive diagnostic procedures as a result of lung cancer screening.⁵²

Although morbidity and mortality rates from these procedures in asymptomatic individuals are not available, mortality rates due to complications from surgical interventions in symptomatic patients range from 1% to 12%, with morbidity rates ranging from 9% to 44%, with higher rates associated with larger resections. Other potential harms of screening are anxiety and concern as a result of positive and false-positive results, as well as possible false reassurance resulting from false-negative results.⁵²

Ovarian cancer—There is adequate evidence that there is no mortality benefit to routine screening for ovarian cancer with single-threshold serum carbohydrate antigen (CA)-125 testing of asymptomatic women, excluding those with known genetic mutations that increase their risk for ovarian cancer.⁵³

Evaluation of abnormal test results consists of either repeated testing or, frequently, removal of one or both ovaries by laparoscopy or laparotomy; and there is adequate evidence that

screening for ovarian cancer can lead to major surgical interventions in women who do not have cancer.⁵³

New evidence about combination of ultrasonography and serological CA-125 test for screening suggests that abnormal test results may result in surgery for a substantial proportion of women who do not have cancer;⁵⁴ and there is high certainty that harms of screening for ovarian cancer outweigh benefits, leading to the recommendation against screening for ovarian cancer in women (**D** recommendation).⁵⁵

Pancreatic cancer—There is no evidence that screening for pancreatic cancer is effective in reducing mortality.⁵⁶ There is little new evidence and no critical ongoing studies of screening for pancreatic cancer, with the literature noting ongoing research about identifying and screening high-risk groups especially with serological markers.⁵⁷ There is a potential for significant harm due to low prevalence of pancreatic cancer, limited accuracy of available screening tests, invasive nature of diagnostic maneuvers, and poor outcomes of treatment.⁵⁶ As a result, harms of screening for pancreatic cancer exceed any potential benefits, and routine screening for pancreatic cancer in asymptomatic adults using serological markers such as CA 19-9 is not recommended (**D** recommendation).

Screening for Substance Abuse

Evidence is insufficient to demonstrate that treatment after use of various illicit drugs reliably improves social and legal outcomes for patients, as treatment cannot be directly linked to longer term improvements in morbidity or mortality (**I** recommendation).⁵⁸ There is fair evidence that stopping or reducing drug misuse is related to reduced morbidity and mortality, although none of this evidence was derived from individuals screened for drug misuse in primary care settings. There is no evidence of harms associated with screening for illicit drug use; however, failure to protect the confidentiality of positive results could potentially affect a patient's employment, insurance coverage or personal relationships.⁵⁸

Adverse events ranging from elevated liver function tests to seizures have been reported in trials of individuals being treated for illicit drug use with opiate agonists, opiate antagonists and antidepressants, with some reported events appearing to be associated with the underlying drug use. Toxicological tests of blood or urine can provide objective evidence of drug use, but they do not distinguish between occasional users and those who are impaired by drug use.⁵⁸

A Benefit to Public Health

It should be noted that the recommendations of the U.S. Preventive Services Task Force (USPSTF) may not be in agreement with some screening recommendations issued by other healthcare organizations due to the fact that they are based on the most rigorous assessment of scientific evidence, leading to many **D** and **I** recommendations. For example, of the 17 cancer screenings evaluated, only three were **A** recommendations while 11 were either **D** (eight instances) or **I** recommendations (see the tables).

Americans tend to be enthusiastic about screening, especially cancer screening.⁵⁹ What could be wrong with screening, especially if it can detect a life-threatening condition at an

earlier stage? Are lives being lost to save money? Costs are, however, rarely the reason that guidelines set limits on screening; rather, it is the balance of potential harms relative to potential benefits. Harms include iatrogenic complications, such as perforation from colonoscopy, anxiety over abnormal results, and a cascade of follow-up tests and treatments.

Screening can precipitate over-diagnosis, resulting in the workup and treatment of conditions that pose little threat to patients' health especially when, given a test's performance characteristics (clinical sensitivity and clinical specificity), a positive test is not adequately predictive of the disease, which is a common situation for many screening tests.

Patients must be adequately informed of the nature and magnitude of the trade-off involved with early detection of disease. It is not possible, however, to predict whether greater awareness of harms will dampen patients' enthusiasm for dubious screening tests.⁵⁹ More realistically, resource limitations will intervene: profligate screening practices will become increasingly unaffordable in a society struggling with spiraling healthcare costs.

Any society's first concern should be to confirm that health screening provides a net benefit to the public's health. This will require that harms be considered independently of costs. Until the reality of harms becomes more palpable to clinicians and the public, concerns about the safety of screened populations will continue to be mistaken for frugality. Furthermore, efforts to control health expenditures should focus not only on the benefits, harms and costs of screening tests, but also on their value; i.e., whether they provide health benefits that are actually worth their costs or harms to health.⁶⁰

Early disease detection through screening may offer an opportunity to treat a disease at a time when a cure or control of the disease is most likely. However, treatment or over-treatment of incidental, clinically insignificant disease may result in a more adverse overall health outcome compared with no treatment at all. Screening may miss early-stage disease, it can detect diseases that are either too advanced or aggressive to respond to treatment, or indolent and not likely to produce clinical symptoms. There is likelihood for several adverse effects of screening complications from additional diagnostic procedures and unnecessary interventions due to false-positive test results; identification and treatment of clinically unimportant disease that would not have become clinically apparent in the person's lifetime, resulting in increased cost of unnecessary screening; and psychological distress, worry and anxiety associated with screening.²

Given the low positive predictive value of many screening tests, a vicious cycle may ensue: screening tests may lead to increased risk perception triggered by positive test results that are likely to lead to more screening, hence resulting in more false-positive results. In this sense, health screening may represent a double-edged sword. On one hand, various diseases or conditions may be diagnosed during their asymptomatic phases, providing an opportunity for clinical and preventive interventions and increasing the likelihood of more favorable health outcomes. On the other hand, over-diagnosis and overtreatment may result, particularly when evidence either points to net harm or it is insufficient, conflicting or supports only a small magnitude of net benefit.

False-positive and false-negative results are present using any screening tests. False-positive rate becomes more relevant when population prevalence decreases; therefore, some screening tests are effective for the high-risk, but not for the general population. False-positive results are not inconsequential as they may lead to disease labeling and its resulting psychological morbidities as well as physical morbidities and mortality that may ensue from additional diagnostic tests and explorations.

Lowering the threshold for disease detection may lead to still greater false-positive rates and interventions against, and treatment for, inconsequential diseases that in the absence of screening may not become clinically apparent and cause any morbidities and mortality during a patient's lifetime. Also, a negative screening test result should not be interpreted as providing a "clean bill of health." This is due to false-negative results and limited sensitivity of all screening tests.

Potential Outcomes

Outcomes for patients undergoing health screening can be divided into several categories:⁵

- those with disease which would have been cured by treatment even when undetected by screening; in these cases, lives may not be improved by screening but earlier detection may impact transmission of some infectious diseases;
- those with incurable disease at the time of screening for whom screening itself may not change treatment or outcome but results may impact family, reproductive and other decisions as well as transmission of some diseases;
- those dying of co-morbidities other than the screened disease; the quality of life may actually be reduced by screening-mediated diagnostic and treatment interventions;
- those who are the main beneficiaries of a screening program with diseases which may be cured or prevented from being transmitted through screening and early detection; and
- those who do not have the disease or condition being screened, usually the largest group. Harms to this group are usually minimal unless morbidity and mortality resulting from screening is significant.

Screening tests have individual and public health implications. The decision to participate in screening can be a matter of individual choice, particularly for diseases or conditions with screening recommendation of **C** or **I**. This choice may hinge on the probability of various outcomes and may depend on the cost of screening and access to it, as well as how individuals feel about them.

Screening may save a few lives and reduce morbidity from progressive disease. A few people may experience disease-specific morbidities and eventually die of the disease anyway. More may face subsequent cascades of diagnostic testing or disease monitoring procedures with uncertainties about presence of the disease. Some may be treated unnecessarily or experience the morbidities and possibly mortality resulting from the treatment. In short, in some cases, whether or not to be screened may be a matter of personal

choice when magnitude of net benefit is small (C recommendation) or when there is insufficient, poor-quality or conflicting evidence supporting a screening test (I recommendation).

While these discussions focused on inappropriate overutilization of screening tests, many clinical laboratory tests are underutilized as recently documented in a systematic review by Zhi, et al.⁶¹ These scientists reported that during 1997-2012, there was an overall average rate of 45% underutilization of laboratory tests compared to an average rate of 21% for overutilization. Pertinent to this report are two conditions, colorectal cancer and chlamydial infections, that are under-represented in health screening despite strong (A) recommendations. Nationally, annual chlamydia screening rate for females aged 15-25 years increased from 25.3% in 2000 to 43.6% in 2006, and then decreased slightly to 41.6% in 2007, well below 50%.⁶² Overall, colorectal cancer screening was 58.6% and still well below the Healthy People 2020 target of 70.5%.⁶³ The USPSTF has not had the resources to evaluate many screening tests, particularly those relating to certain high-risk populations that, due to their size, do not represent a significant societal burden of suffering. Additionally, the Task Force, in their evaluation of population-based screening tests, has focused on primary and secondary prevention as opposed to tertiary prevention and clinical intervention. However, other specialty healthcare organizations should consider using the evidence-based and rigorous evaluation methods of the USPSTF⁴ to develop similar recommendations for tertiary prevention.

Publication and dissemination of laboratory practice recommendations and guidelines is necessary but not sufficient for quality improvement in clinical laboratory practice. Various methods should be tried to promote evidence-based and accepted standards of laboratory practice and their effectiveness should be evaluated. The approaches that laboratory professionals have used to impact optimal utilization of laboratory services have included promotion of evidence-based laboratory recommendations and guidelines, provision of continuing medical education, periodic clinician feedback, provision of electronic reminders and decision-support systems, appropriate changes in laboratory test ordering systems, and linking clinical decision support tools to electronic health systems to decrease errors of omission.⁶⁴ Studies should be devised to assess what the motivators and barriers are for adoption of good laboratory practices and to how best promote them, including exploration of reasons for not following accepted standards of practice so that root causes for non-adherence could be identified and addressed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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